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Amygdala atrophy is prominent in early Alzheimer's disease and relates to symptom severity

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ABSTRACT

Despite numerous studies on the role of medial temporal lobe structures in Alzheimer's disease (AD), the magnitude and clinical significance of amygdala atrophy have been relatively sparsely investigated. In this study, we used magnetic resonance imaging (MRI) to compare the level of amygdala atrophy to that of the hippocampus in very mild and mild AD subjects in two large samples (Sample 1 $n=90$; Sample 2 $n=174$). Using a series of linear regression analyses, we investigated whether amygdala atrophy is related to global cognitive functioning (Clinical Dementia Rating Sum of Boxes: CDR-SB; Mini Mental State Examination: MMSE) and neuropsychiatric status. Results indicated that amygdala atrophy was comparable to hippocampal atrophy in both samples. MMSE and CDR-SB were strongly related to amygdala atrophy, with amygdala atrophy predicting MMSE scores as well as hippocampal atrophy, but predicting CDR-SB scores less robustly. Amygdala atrophy was related to aberrant motor behavior, with potential relationships to anxiety and irritability. These results suggest that the magnitude of amygdala atrophy is comparable to that of the hippocampus in the earliest clinical stages of AD, and is related to global illness severity. There also appear to be specific relationships between the level of amygdala atrophy and neuropsychiatric symptoms that deserve further investigation.

1. Introduction

By the time patients exhibit the hallmark amnesic syndrome of Alzheimer's disease (AD), neuropathology has usually decimated medial temporal lobe (MTL) structures (Braak and Braak, 1991). In vivo evidence for this process can be plainly seen by viewing magnetic resonance images. Extensive investigations have demonstrated quantitative morphometric abnormalities of the hippocampal formation, entorhinal cortex, and perirhinal cortex early in the illness (prior to dementia). Furthermore, these abnormalities correlate with the overall severity of clinical impairment and are specifically related to episodic memory deficits (Di Paola et al., 2007). In post-mortem studies, amyloid (senile) plaques, neurofibrillary tangles, and neuronal loss have all been observed in the amygdala (Herzog and Kemper, 1980; Tsuchiya and Kosaka, 1990; Scott et al., 1991; Arriagada et al., 1992; Scott et al., 1992). Although these post-mortem studies have called attention to similar neuropathological abnormalities in the amygdala as are found in the hippocampus, there has been far less in vivo investigation of amygdala atrophy and its clinical correlates in AD.

With respect to amygdala atrophy in early AD, several important anatomic and clinical questions remain incompletely answered. First, across the 13 published studies of amygdala atrophy in AD, findings regarding the magnitude of atrophy have been very inconsistent, with reports of atrophy ranging from 15% to 41% compared to older controls (OC). Furthermore, it is unclear whether the magnitude of amygdala atrophy is greater than (Cuenod et al., 1993; Lehericy et al., 1994; Mori et al., 1997; Krasuski et al., 1998; Basso et al., 2006), less than (Jack et al., 1997; Callen et al., 2001; Horinek et al., 2006; Farrow et al., 2007), or similar to (Killiany et al., 1993; Mizuno et al., 2000; Barnes et al., 2006; Schultz et al., 2009) that of the hippocampus.

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Given the substantial variability in the frequency and types of socioaffective symptoms in AD, it seems reasonable to hypothesize that the amygdala would be more variably affected within a sample of AD patients than the hippocampus. Second, although amygdala atrophy has been shown to relate to global illness severity in AD (Jack et al., 1997; Mizuno et al., 2000), there has been little investigation comparing the strength of this relationship with that of the hippocampus. Since the size of these structures is collinear, it is important to try to understand which of them is most strongly related to illness severity and whether the amount of atrophy in the other explains additional variance in overall symptom severity. We hypothesized that hippocampal atrophy is most strongly related to illness severity but that the amount of amygdala atrophy present would explain additional variance in illness severity beyond that explained by the hippocampus. Finally, although behavioral (psychiatric) symptoms are a major contributor to patient-family dysfunction and distress in AD, there has been surprisingly little effort to investigate whether amygdala atrophy relates to this domain of symptoms. The only study to specifically examine the relation between amygdala atrophy and psychiatric symptoms in mild AD reported no relationship (Horinek et al., 2006).

In the present study, we used automated measurements of in-vivo human brain volumes derived from magnetic resonance imaging (MRI) to investigate the magnitude and consistency of amygdala atrophy in two large and independent samples of patients with AD (and older controls). The main goal of having a second sample in this study design was to demonstrate the reliability of the findings, supporting their generalizability. Both samples included a large number of patients with very mild (CDR = 0.5) and mild (CDR = 1) AD, allowing for measurement of amygdala atrophy early in the illness. To address the question of whether the amygdala shows comparable atrophy to the hippocampus, the magnitude and variance of atrophy in the two structures were compared.

Second, we explored the clinical significance of amygdala atrophy in mild AD, investigating the relationship between amygdala atrophy and cognitive function using the Mini Mental State Examination (MMSE) and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB). In addition, to try to determine the specificity of the relationship, we performed an additional analysis controlling for hippocampal volume. The goal of these analyses was to determine whether the magnitude of amygdala atrophy is a reflection of global severity of the illness and whether it accounts for illness severity beyond its shared variance with hippocampal atrophy.

Finally, to address questions regarding specific relationships between amygdala atrophy and types and severity of neuropsychiatric symptoms in AD, data from the Neuropsychiatric Inventory (NPI) were analyzed. Animal and human studies have suggested that amygdala lesions are associated with agitation/aggression and irritability (less) (Wright et al., 2007), anxiety (less)(Davidson, 2002), and apathy (more) (Kile et al., 2009). Data are conflicting in regard to depression (Omura et al., 2005). We examined the level of amygdala atrophy in AD patients with either no, mild or moderate/severe impairment using the NPI items reflecting these symptoms, testing hypotheses based on prior findings as well as exploring the current data *de novo*.

2. Method

2.1. Participants

Sample 1. This sample consisted of AD and OC participants in a longitudinal study at the Washington University Alzheimer's Disease Research Center, conducted in accordance with guidelines of the Washington University Human Studies Committee. There were 177 subjects (60 males and 117 females; mean age 77.4 ± 7.3; mean education 14.0 ± 2.2). Data from subsets of these subjects have been published in previous studies (Buckner et al., 2004; Salat et al., 2004; Fotenos et al., 2005). At study enrollment, subjects with non-AD disorders that could potentially cause dementia, active neurologic or psychiatric illness, serious head injury, clinical history of stroke, gross anatomical abnormalities on MRI and use of psychoactive drugs were excluded (Marcus et al., 2007). Participants underwent detailed structured evaluations, including a health history, depression inventory, aphasia battery and medication inventory, MMSE, CDR. Diagnostic criteria for AD required the gradual onset and progression of impairment in memory and in at least one other cognitive and functional domain, comparable to standard diagnostic criteria for probable AD (McKhann et al., 1984).

Sample 2. This sample consisted of AD and OC participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (www.loni.ucla.edu/ADNI). There were 367 subjects (192 males and 175 females; mean age 75.5 ± 6.2; mean education 15.5 ± 3.0). The ADNI was launched in 2003 by the NIA, the NIBIB, the FDA, private pharmaceutical companies and non-profit organizations, as a $60-million, 5-year public–private partnership. The primary goal of ADNI has been to test whether imaging measures, biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

All subjects underwent thorough clinical and cognitive assessment, including MMSE, CDR, and NPI. The diagnosis of AD was made if the subject had a MMSE score between 20 and 26, CDR score of 0.5 or 1, and met NINCDS/ADRDA criteria for probable Alzheimer's disease. The OC had MMSE scores between 28 and 30, a global CDR of 0, and no symptoms of depression, MCI, or other forms of dementia. Subjects were excluded if they had any serious neurological disease other than incipient AD, any history of brain lesions or head trauma, or psychoactive medication use. The study was conducted with written informed consent according to Good Clinical Practice, the Declaration of Helsinki and U.S. 21 CFR Part 50-Protection of Human Subjects, and Part 56-Institutional Review Boards.

2.2. Magnetic resonance imaging data acquisition and analysis

Sample 1. For each subject, multiple (3 or 4) high-resolution structural T_1-weighted magnetization-prepared rapid gradient echo (MP-RAGE) images were acquired entry on a 1.5 T Siemens Medical Systems scanner with the following parameters: repetition time (TR) 9.7 ms, echo time (TE) 4 ms, flip angle (FA) 10°, inversion time (TI) 20 ms, voxel size 1 × 1 × 1.25 mm. These data have been made openly available to the scientific community (http://www.oasis-brains.org/).

Sample 2. For each subject, 2 high-resolution structural T_1-weighted MP-RAGE images were acquired either on a 1.5 T General Electric Healthcare, a 1.5 T Siemens Medical Solutions or a 1.5 T Phillips Medical System scanner. Acquisition parameters were as follows: TR 2400 ms, TE minimum full time excitation, FA 8°, TI 1000 ms, voxel size 1.25 × 1.25 × 1.2 mm. These data have been made available to the scientific community (http://www.loni.ucla.edu/ADNI/).

Volumetric analysis was performed using Freesurfer software (http://surfer.nmr.mgh.harvard.edu) as previously described in detail (Fischl et al., 2002). Briefly, for each subject, the multiple structural scans were motion corrected and averaged to create a single volume. The resulting averaged volume was used to segment cerebral white matter and deep gray matter structures (including hippocampus and amygdala) (Fig. 1). This segmentation procedure automatically assigned a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set. This probability is based on the voxel's location in the volume, the neighboring voxels' tissue classes, and the intensity value in each voxel. The technique has previously been shown to be comparable in accuracy to manual labeling (Fischl et al., 2002). For each subject, we visually inspected the segmentation of the amygdala and determined whether it was acceptable according to standard anatomic criteria as we have employed in prior studies (Wright et al.,